Risk Factors and Outcomes of Daptomycin Non-susceptible Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infections

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ABSTRACT

Introduction
Daptomycin has been approved and successfully used for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. However, reports of daptomycin non-susceptible (DNS) MRSA strains have emerged over the recent years. This study describes the clinical characteristics of patients with DNS MRSA bloodstream infections (BSIs) with the objective of identifying risk factors and outcomes.

Methods
This is a retrospective case-control study in a tertiary healthcare system in southeast Michigan. Cases included 34 patients with DNS MRSA BSI between 9/24/2005 and 3/31/2018. Cases were matched with controls with MRSA BSI based on age, source of BSI, and time-period of BSI in a 1:1 ratio. Charts were reviewed for clinical and laboratory data. Vancomycin (van) and dap minimum inhibitory concentrations (MICs) were determined by E-test. DNS was defined as an MIC >1.0 µg/mL. Chi-square test, Fisher's Exact test and t-test were used to determine statistical significance.

Results
In the case cohort, the source of BSI was endovascular in 11(32%) patients, central-line associated in 3(9%), secondary BSI in 13(38%), and unclear in 7(21%). Table 1 summaries the results.

Conclusion
Prior exposure to dap and van therapy, and high van MIC in MRSA isolates are risk factors for DNS MRSA BSI. DNS is associated with statistically higher risk of 90-day MRSA BSI recurrence

BACKGROUND

- Methicillin-Resistant Staphylococcus aureus bloodstream infections continue to carry high morbidity and mortality despite advances in medical treatment[1].
- Daptomycin, a lipopeptide antibiotic with concentration-dependent bactericidal activity was approved by the FDA for therapy of S. aureus bacteremia and infective endocarditis in 2005.
- Since then, several cases of therapy failure associated with the emergence of of DNS MRSA strains have been documented.
- Although the prevalence is low, S. aureus strains with reduced susceptibility to daptomycin pose a significant clinical challenge in treatment.
- Previous data shows possible cross-resistance to daptomycin amongst S. aureus strains with reduced susceptibility to vancomycin
- Data on the clinical risk factors and outcomes of daptomycin-nonsuceptible MRSA bacteremia is scarce.

OBJECTIVE

This study describes the clinical characteristics of patients with DNS MRSA bloodstream infections (BSIs) with the objective of identifying risk factors and outcomes.

METHODS

- This is a retrospective case-control study in a tertiary healthcare system in southeast Michigan.
- Cases included all non-duplicate patients with DNS MRSA BSI between 9/24/2005 and 3/31/2018. A total of 34 patients were included.
- Cases were matched in a 1:1 ratio with controls with MRSA BSI based on age, source of BSI, and time-period of BSI.
- Charts were reviewed for clinical and laboratory data.

METHODS (cont.)

- Vancomycin and daptomycin MICs were determined by E-test according to manufactures instructions (bioMerieux, Inc., Durham NC). DNS was defined as an MIC >1.0 µg/mL.
- Chi-square test, Fisher's Exact test and t-test were used to determine statistical significance.
- Pulsed-field gel electrophoresis was performed on the case isolates and compared using BioNumerics software (Applied Maths, Belgium) with CDC MRSA strains USA100-1100. Isolates were placed in the same PFGE strain group if their SmaI restriction patterns were ≥ 80% similar.

RESULTS

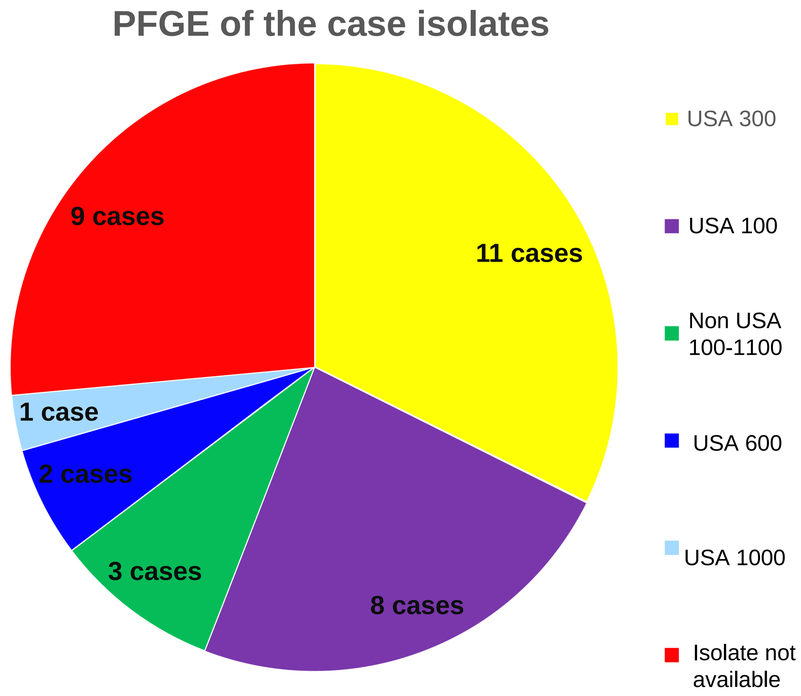
In the case cohort, out of 34 patients, the source of BSI was:

- Endovascular in 11(32%) patients
- Central-line associated in 3(9%) patients
- Secondary BSI in 13(38%) patients
- Unknown in 7(21%) patients
- 18(53.9%) patients where diabetic, 9(27.3%) were on Hemodialysis vs 14(41.2%) and 3(8.8%) were diabetic and on hemodialysis respectively in the control cohort.

Table 1. Clinical characteristics and outcomes of cases and controls.

	Cases N=34(%)	Controls N=34(%)	p-value
Mean age (SD)	63.5 (12.0)	61.9 (11.2)	0.572
Male	18 (52.9)	21 (61.8)	0.462
Mean bacteremia duration in days (SD)	4.4 (3.2)	5.9 (4.9)	0.195
Mean LOS in days (SD)	19.5 (13.6)	18.4 (14.6)	0.751
Mean van MIC (SD)	2.04 (1.19)	1.39 (0.36)	**0.003**
Mean dap MIC (SD)	2.69 (1.32)	0.57 (0.24)	**<0.0001**
Epidemiologic acquisition			
Community-acquired	0	9 (26.5)	**0.002**
Healthcare-associated	21 (63.6)	22 (64.7)	0.927
Hospital-acquired	12 (36.4)	3 (8.8)	**0.007**
90-day prior dap exposure in days	23 (82.1)	3 (9.7)	**<0.0001**
Mean prior dap exposure in days	23.6 (21.0)	2.68 (10.6)	**<0.0001**
90-day prior van exposure in days	25 (89.3)	9 (29)	**<0.0001**
Mean prior van exposure in days	13.0 (14.7)	4.19 (12.7)	**0.020**
In-hospital mortality	9 (27.3)	4 (11.8)	0.108
30-day mortality*	10 (32.3)	6 (18.8)	0.218
90-day mortality*	12 (38.7)	6 (21.4)	0.150
Mean CCI (SD)	5.7 (3.07)	4.4 (2.9)	0.077
90-day MRSA BSI recurrence*	8 (44.4)	2 (9.5)	**0.025**

* From date of index BSI
CCI = Charlson Comorbidity index



- 12 cases had the initial MRSA isolate available for testing, and for each of the 12 cases, the MRSA strain PFGE remained the same over time .

CONCLUSIONS

- **This is the largest study aiming to analyze the risk factors and outcomes of patients with daptomycin-nonsusceptible MRSA bloodstream infections.**
- **DNS MRSA BSI is primarily a health-care related infection.**
- **Elevated MIC to vancomycin is associated with daptomycin resistance.**
- **Prolonged exposure to vancomycin and/or daptomycin is associated with daptomycin resistance**
- **Daptomycin resistance is associated with a significantly higher 90-day recurrence rate.**

FUTURE DIRECTIONS

- DNA sequencing for analysis of resistance mechanisms
- In vitro antibiotic susceptibility and synergy studies.

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